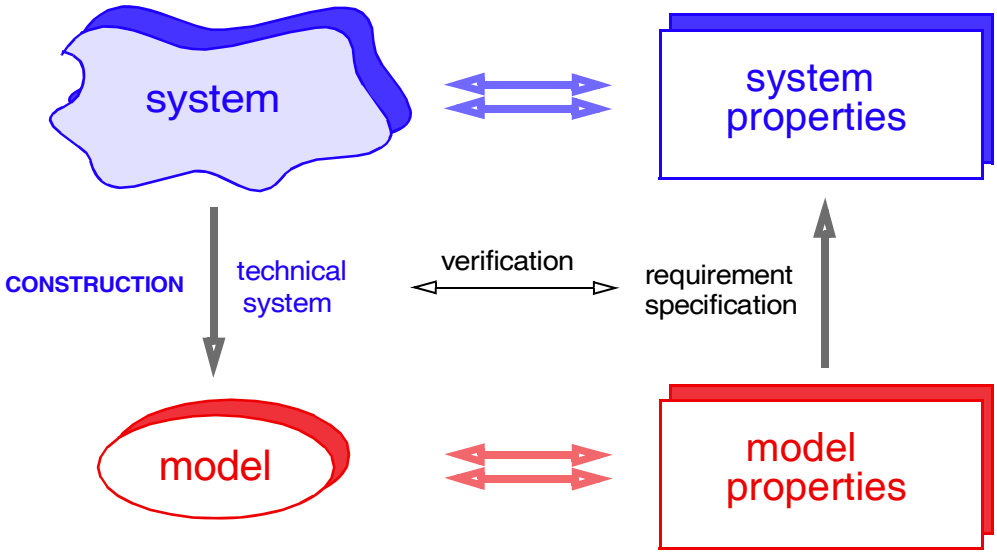
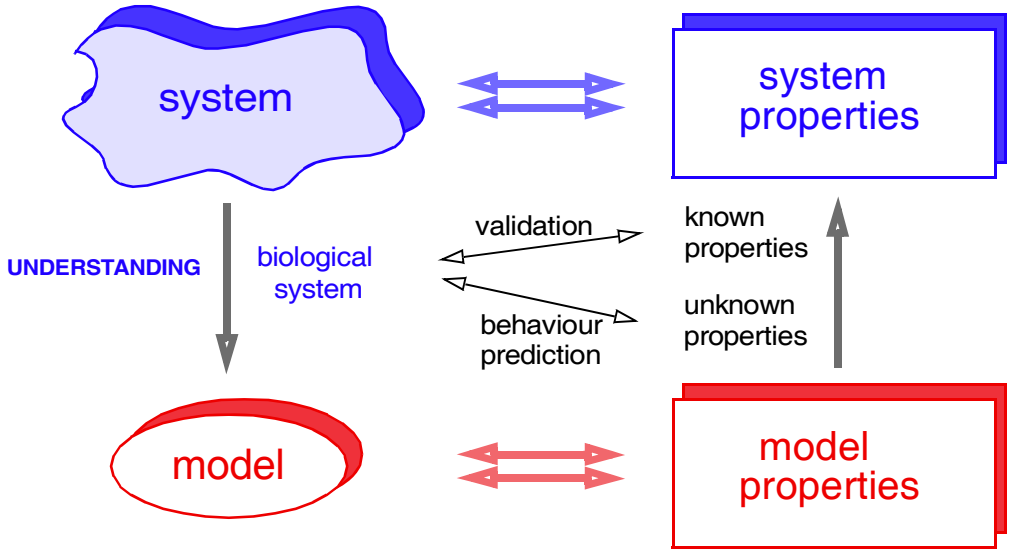
BIOCHEMICALLY INTERPRETED PETRI NETS - TWO OPEN PROBLEMS

(RELATIONS BETWEEN TIME-FREE AND TIME-DEPENDENT PETRI NETS)

Monika Heiner

INRIA / Rocquencourt, projet CONTRAINTES
on sabbatical leave from BTU Cottbus, Dept. of CS





STRUCTURE OF THE TALK

- **introduction**
  - -> *What are biochemically interpreted Petri nets ?*
    - *how do they look like ?*
    - *a typical analysis technique - the T-invariants*
    - *some examples*
- **two open problems**
  - -> *time-dependent boundedness* -> *weakly bounded*
  - -> *time-dependent liveness* -> *weakly live*

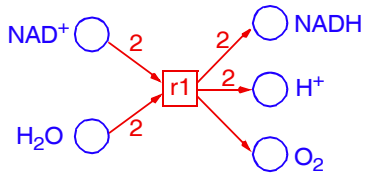
BIOCHEMICALLY INTERPRETED PETRI NETS

monika.heiner@informatik.tu-cottbus.de

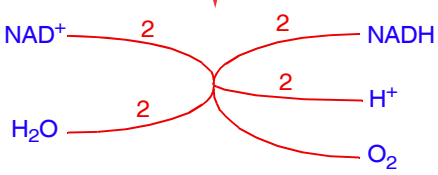
BIO PETRI NETS, BASICS

- **chemical reaction**

$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$

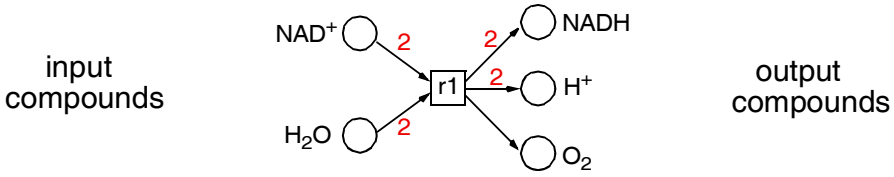


hyper-arcs

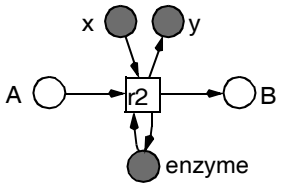


- **chemical reactions -> atomic actions -> Petri net transitions**

$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$

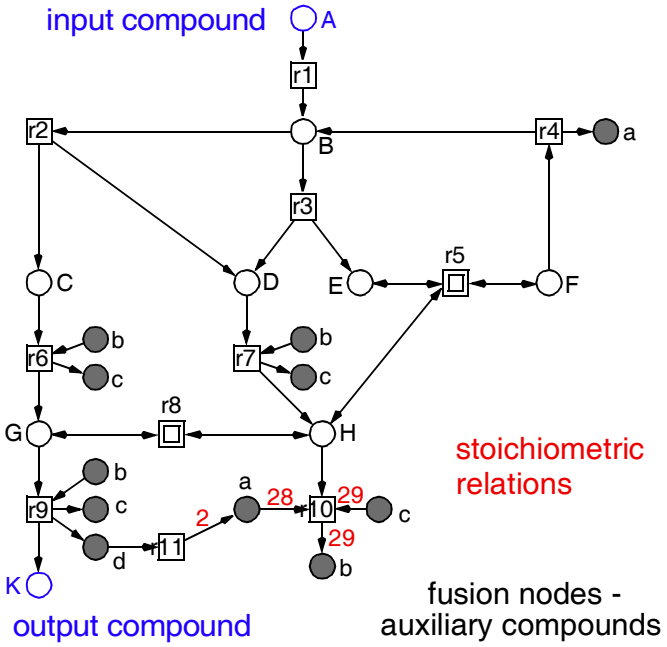


- **chemical compounds -> Petri net places**
  - *primary compounds* - *metabolites*
  - *auxiliary compounds, ubiquitous -> fusion nodes* - *e. g. electron carrier*
  - *catalyzing compounds* - *enzymes*



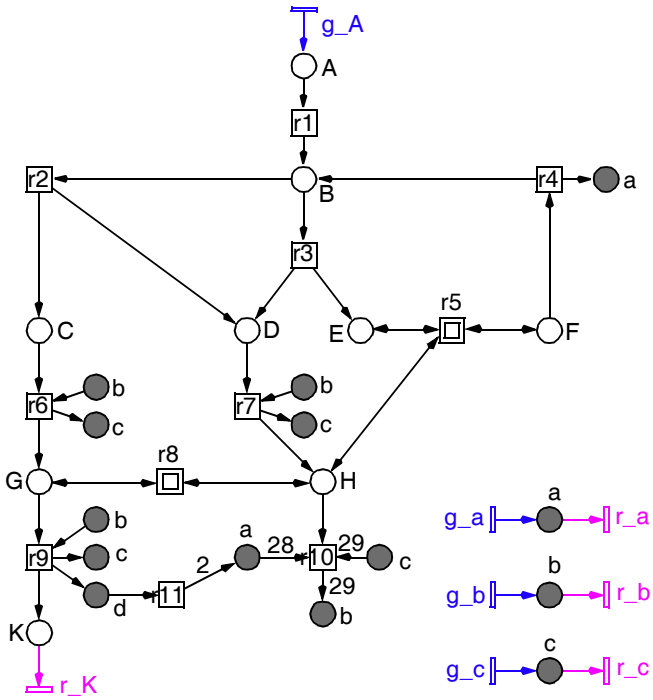
- **stoichiometric relations -> Petri net arc multiplicities**
- **compounds distribution -> marking**

r1: A -> B
r2: B -> C + D
r3: B -> D + E
r4: F -> B + a
r5: E + H <-> F
r6: C + b -> G + c
r7: D + b -> H + c
r8: H <-> G
r9: G + b -> K + c + d
r10: H + 28a + 29c -> 29b
r11: d -> 2a



BIO PETRI NETS, WITH ENVIRONMENT BEHAVIOUR

- **input substances**
  -> *generating pre-transitions*
- **output substances**
  -> *consuming post-transitions*
- **auxiliary substances**
  -> *both*
- **no boundary places, but boundary transitions**
- **transitions without pre-places**
  -> *live*
  -> *all post-places are unbounded*
- **steady state behaviour**
  -> *empty marking reproduction*



BIOCHEMICAL PETRI NETS, SUMMARY

- **biochemical networks**
  -> *networks of (abstract) chemical reactions*
- **biochemically interpreted Petri net**
  -> *partial order sequences of chemical reactions (= elementary actions) transforming input into output compounds / signals*
  [respecting the given stoichiometric relations, if any]
  -> *set of all pathways (self-contained partial order sequence) from the input to the output compounds / signals*
  [respecting the stoichiometric relations, if any]
- **typical properties**

INA

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
N	N	N	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	N

DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S
N	N	Y	N	N	Y	N	?	N	N	Y	?	N

CLAIMS

BIO PETRI NETS - A TYPICALLY ANALYSIS TECHNIQUE

monika.heiner@informatik.tu-cottbus.de

T-INVARIANTS, BASICS

- **Lautenbach, 1973** -> **Schuster, 1993**
- **T-invariants** -> *multisets of transitions*
  - -> *integer solutions x of* $Cx = 0, x \neq 0, x \geq 0$ -> *Parikh vector*
- **minimal T-invariants**
  - -> *there is no T-invariant with a smaller support* -> *sets of transitions*
  - -> *gcD of all entries is 1*
- **any T-invariant is a non-negative linear combination of minimal ones**
  - -> *multiplication with a positive integer*
  - -> *addition*
  - -> *Division by gcD*

$$kx = \sum_i a_i x_i$$

- **Covered by T-Invariants (CTI)** -> **consistency criterion**
  - -> *each transition belongs to a T-invariant*
  - -> *BND & LIVE => CTI*

monika.heiner@informatik.tu-cottbus.de

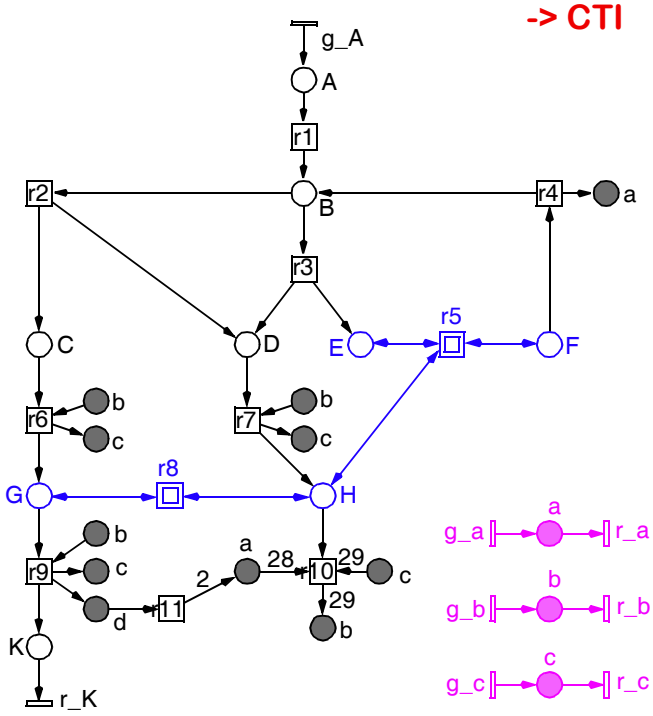
trivial min. T-invariants (5)

-> CTI

- boundary transitions of auxiliary compounds
  -> *(g_a, r_a), (g_b, r_b), (g_c, r_c)*
- reversible reactions
  -> *(r5, r5_rev), (r8, r8_rev)*

non-trivial min. T-invariants (7)

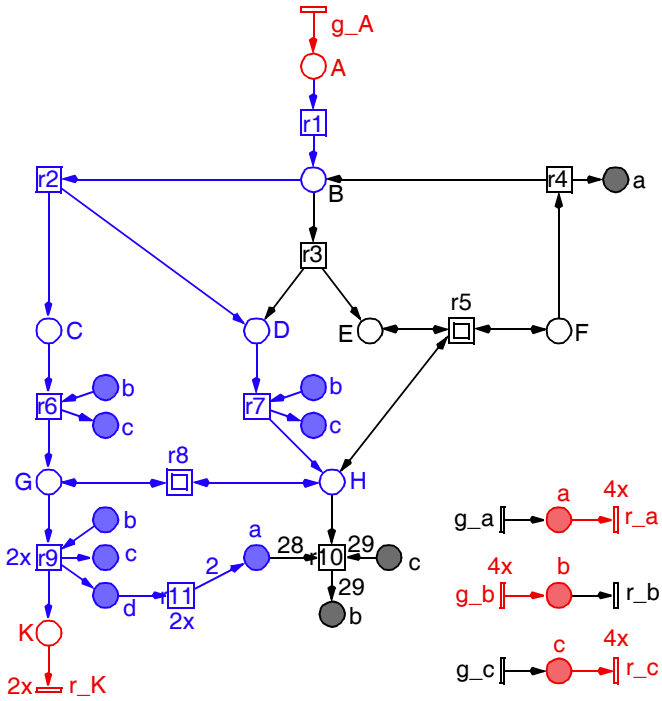
- covering boundary transitions of input / output compounds
  -> *i/o-T-invariants*
- inner cycles



- i/o-T-invariant, example

```
12 |   0.r1          :  1
   |   1.r2          :  1,
   |   3.r8_rev      :  1,
   |   4.r6          :  1,
   |   5.r7          :  1,
   |   9.r9          :  2,
   |   12.r11        :  2,
   |   13.g_A        :  1,
   |   14.r_K        :  2,
   |   15.g_b        :  4,
   |   18.r_c        :  4,
   |   20.r_a        :  4
```

- sum equation
  A + 4b -> 2K +4a + 4c

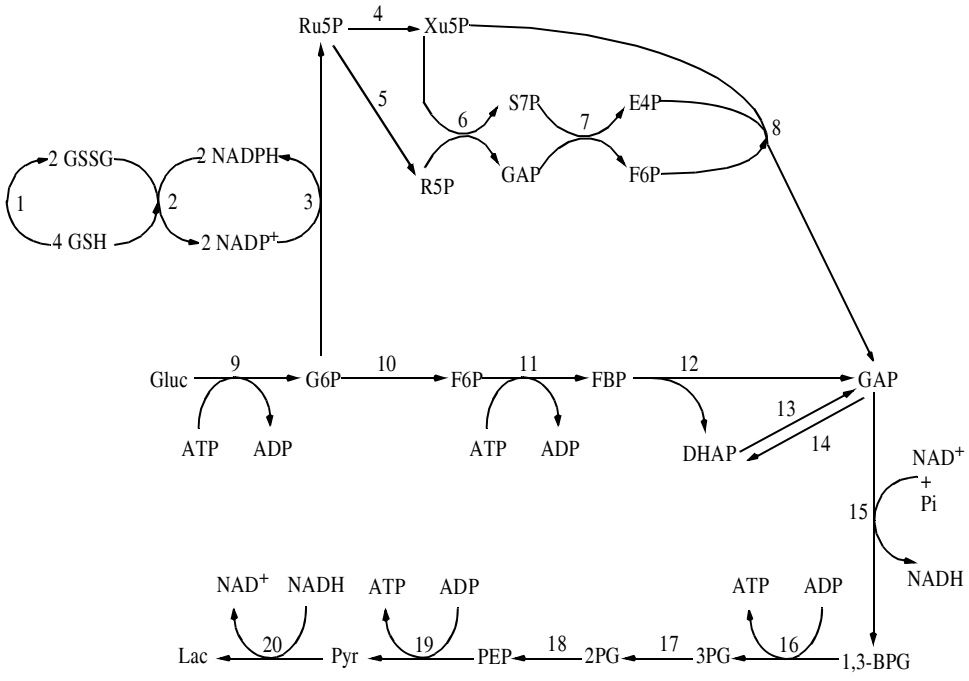


BIO PETRI NETS - SOME EXAMPLES

monika.heiner@informatik.tu-cottbus.de

Ex1 - Glycolysis and Pentose Phosphate Pathway

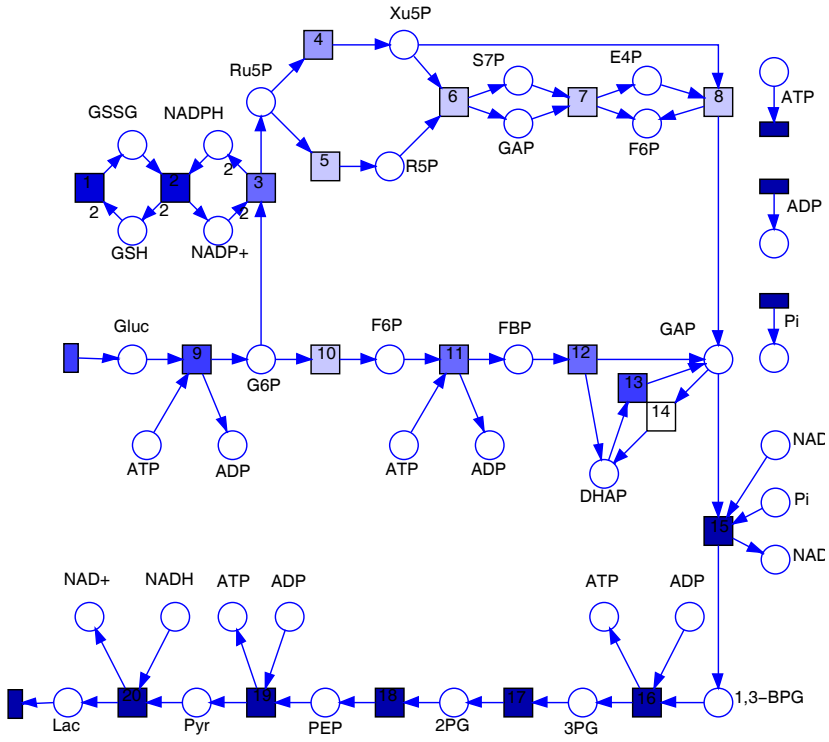
[Reddy 1993]



monika.heiner@informatik.tu-cottbus.de

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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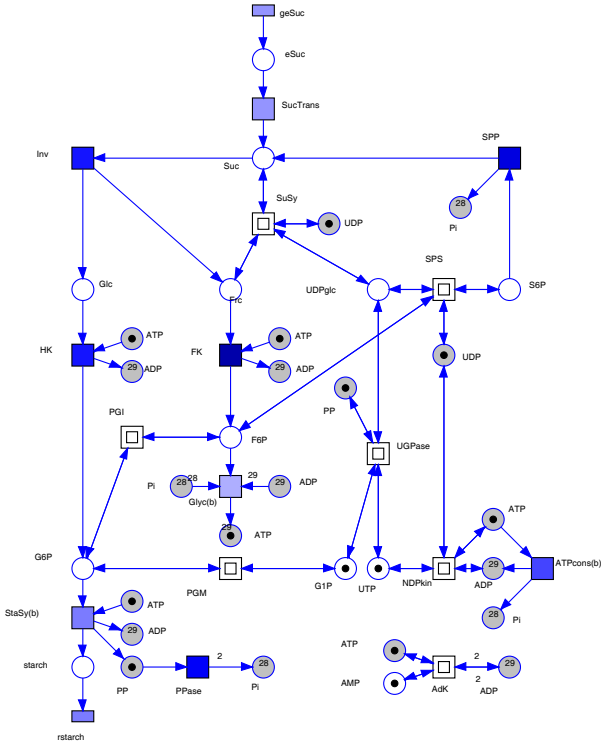
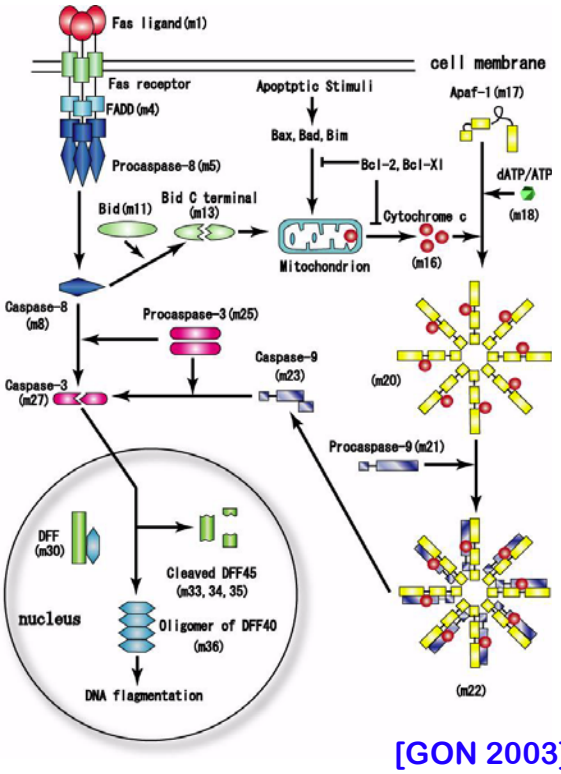
Ex2 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]

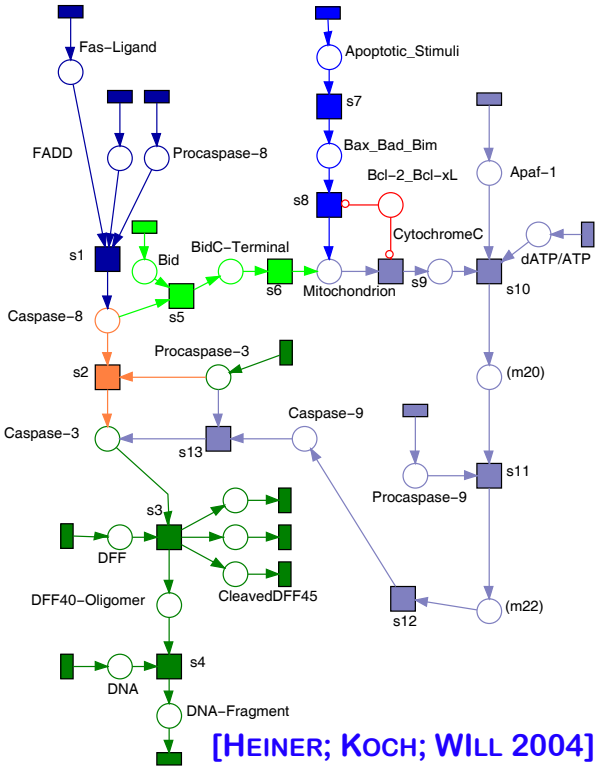


monika.heiner@informatik.tu-cottbus.de

EX3: APOPTOSIS IN MAMMALIAN CELLS



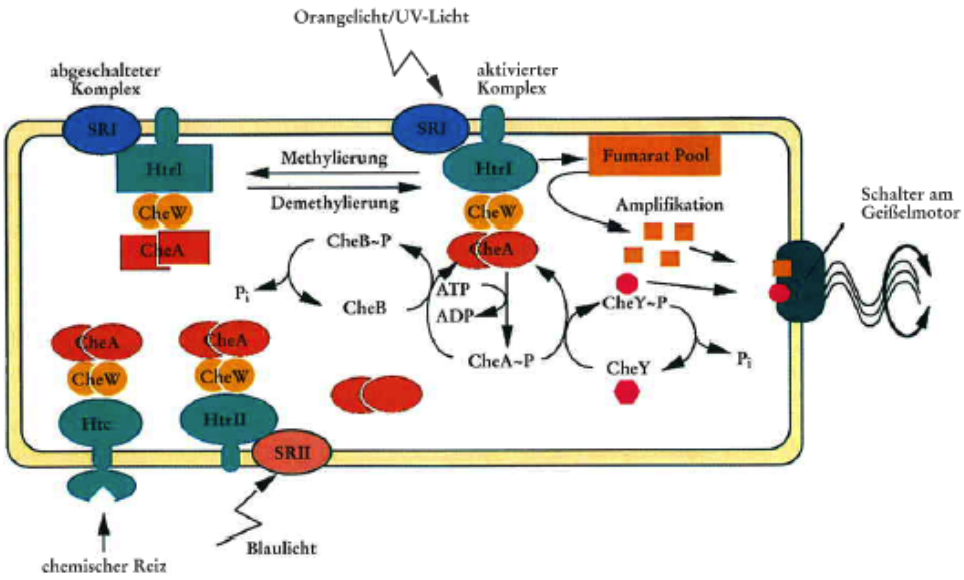
[GON 2003]



[HEINER; KOCH; WILL 2004]

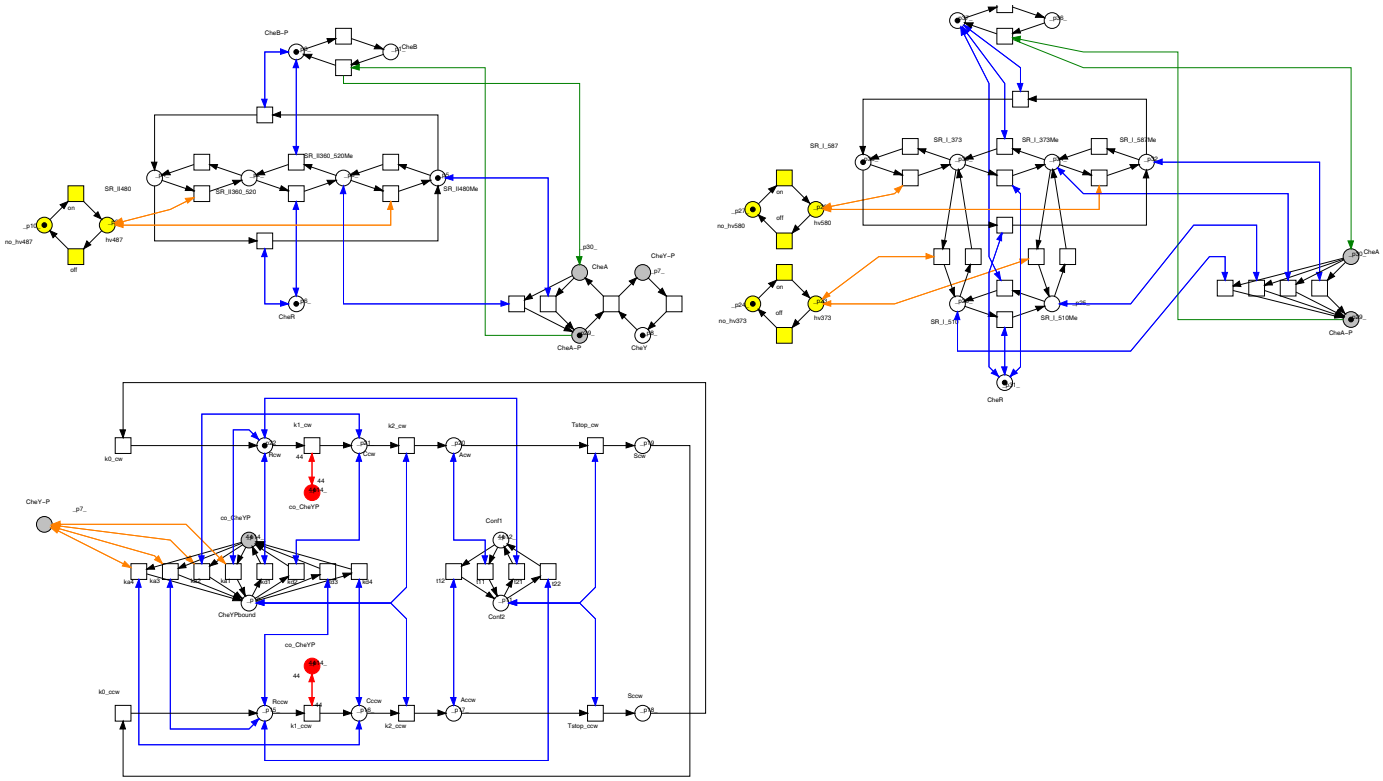
monika.heiner@informatik.tu-cottbus.de

EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM



[Marwan; Oesterhelt 1999]

monika.heiner@informatik.tu-cottbus.de



monika.heiner@informatik.tu-cottbus.de

PN & Systems Biology

PROBLEM 1:

TIME-DEPENDENT BOUNDEDNESS

monika.heiner@informatik.tu-cottbus.de
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T-INVARIANTS, INTERPRETATIONS

- **T-invariants = (multi-) sets of transitions = Parikh vector**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*

- **two interpretations**
  1. *partially ordered transition sequence* **-> behaviour understanding**
     of transitions occuring one after the other
     -> *substance / signal flow*
  2. *relative transition firing rates*
     of transitions occuring permanently & concurrently
     -> *steady state behaviour*

- **a T-invariant defines a subnet** **-> partial order structure**
  - -> *the T-invariant's transitions (the support),*
    + all their pre- and post-places
    + the arcs in between
  - -> *pre-sets of supports = post-sets of supports*

TIME-DEPENDENT BOUNDEDNESS

- **given: time-free Petri net**
  - -> *unbounded*
  - -> *live (supposed to be)*

- **wanted: corresponding time-dependent Petri net**
  - -> *bounded*
  - -> *(still) live*

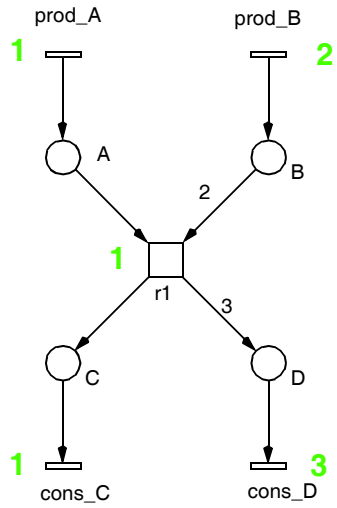
- **relative transition firing rates**
  - -> *may be implemented by transition firing times (constant / interval)*

- **claim**
  - -> *transformation preserves all possible behavior (= minimal T-invariants)*

- **guess**
  - -> *transformation reflects the steady state, so the model should become bounded*

TRANSFORMATION, EX1

A + 2 B -> C + 3 D



T-INVARIANT

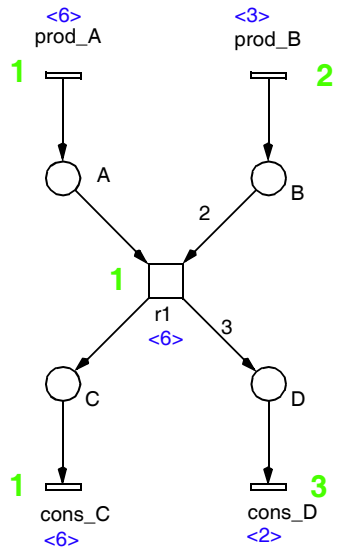
-> properties as time-free net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   N   N   Y   N   ?   N   Y   Y   Y   N
```


TRANSFORMATION, EX1

PN & Systems Biology

A + 2 B -> C + 3 D

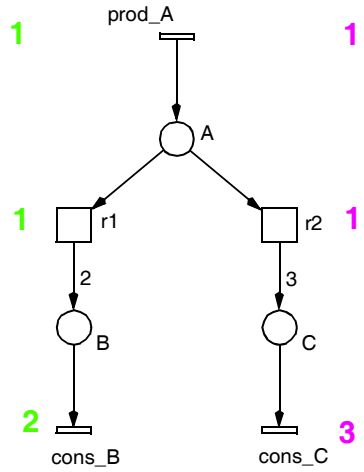


T-INVARIANT

-> properties as time net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   Y   N   N   N   ?   N   Y   Y   Y   N
```

A ->2 B, A -> 3 C



T-INVARIANT1
T-INVARIANT2

-> properties as time-free net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI B   SB  REV DSt BSt DTr DCF L   LV L&S
 N   Y   N   N   Y   N   ?   N   N   Y   Y   N
```


TRANSFORMATION, EX2

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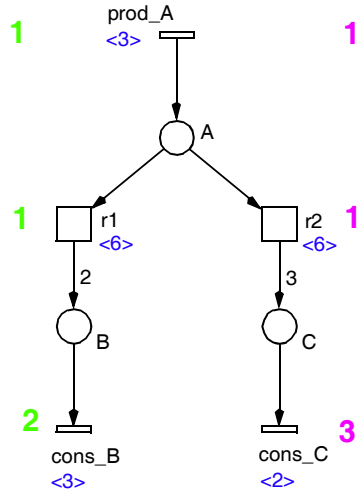
A ->2 B, A -> 3 C



T-INVARIANT1
T-INVARIANT2

-> properties as time net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI B   SB  REV DSt BSt DTr DCF L   LV L&S
 N   Y   Y   N   N   N   ?   N   Y   Y   Y   N
```

monika.heiner@informatik.tu-cottbus.de

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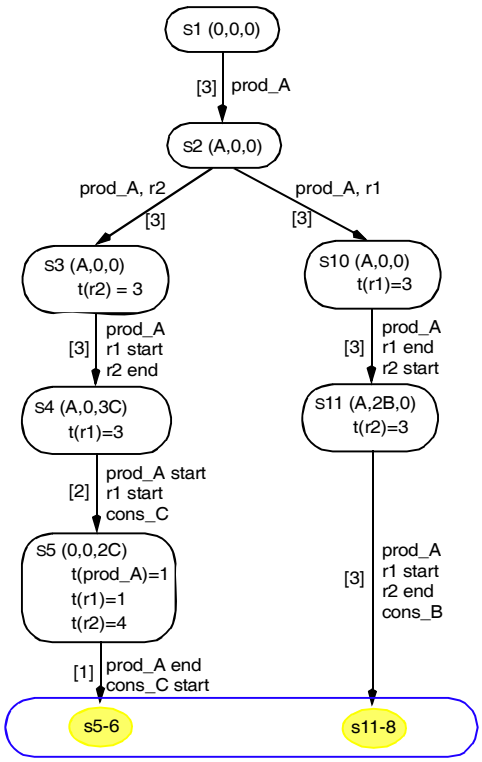
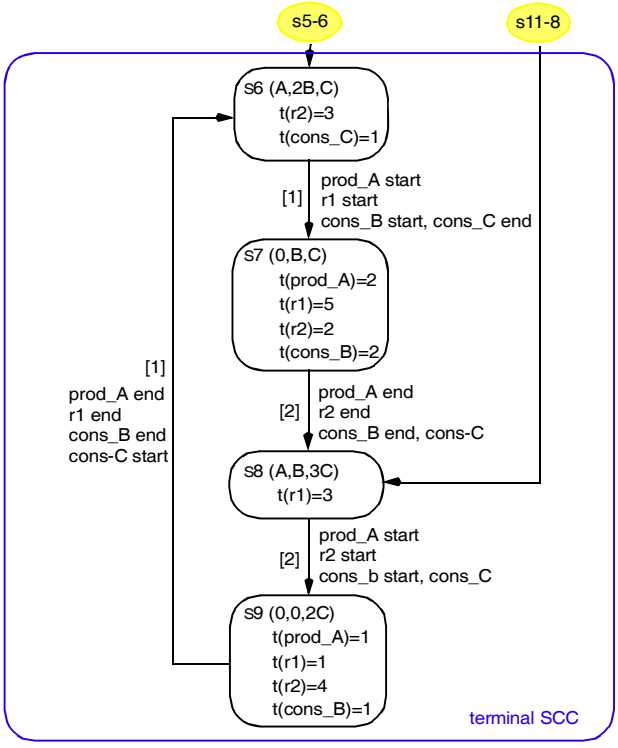
RG(Ex2), Part 1

- transient state



RG(Ex2), Part 2

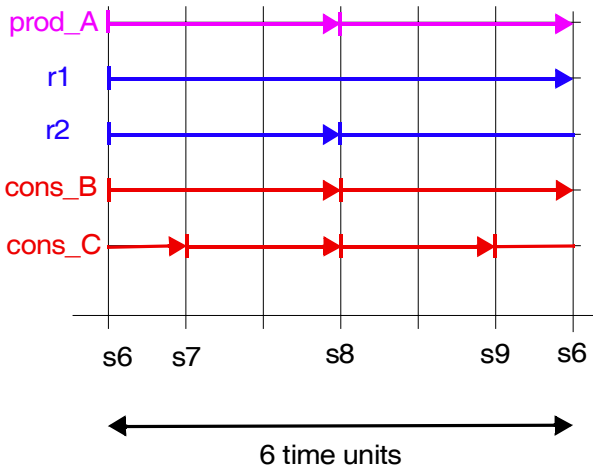
- steady state



RG(EX2), TERMINAL SCC

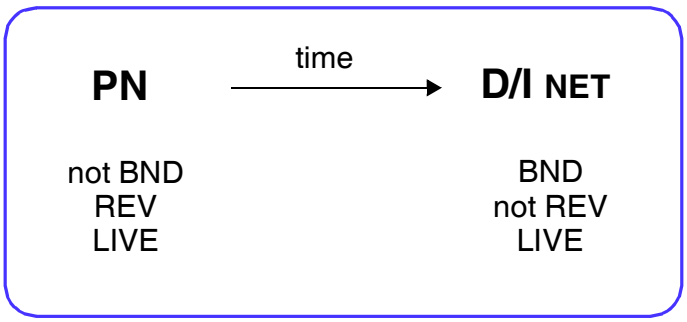
- **contains all transitions**
  - -> *always running*
  - -> *start / end at different time points*
- **contains all minimal t-invariants**
- **timing diagram**
- **relative transition firing rates**

prod_A	:	1	+		1
r1	:	1	**r2**	:	1
cons_B	:	2	**cons_C**	:	3



EX1+ EX2, SUMMARY

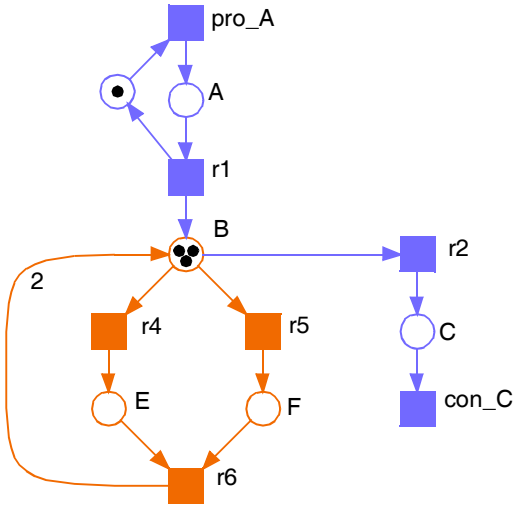
- CTI,
  but not CPI
- transient state
  - -> *initial behaviour to reach steady state*
  - -> *not REV*
  - -> *generally, not DCF*
- steady state behaviour
  - -> *terminal scc*
  - -> *here, BND*
  - -> *here, DCF*

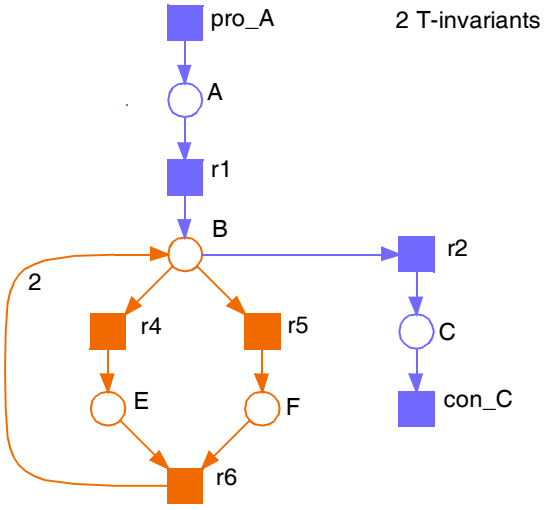


HOWEVER,
THIS DOES NOT ALWAYS WORK !

COUNTEREXAMPLE 1

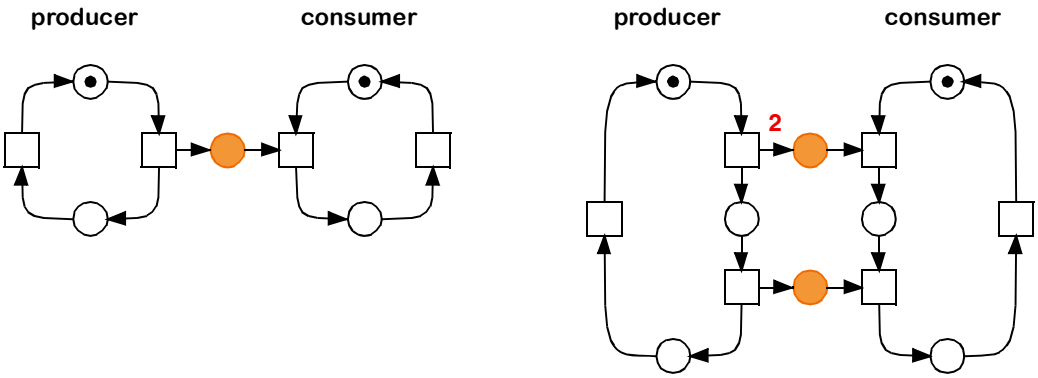
1-duration for all transitions;
FC, there are no deadlocks, traps, p-invariants, besides the pseudo-P-invariant (A , co_A);





BND & LIVE for the given initial marking

COUNTEREXAMPLE 2



weakly bounded

not weakly bounded

[DESEL 2006], WEAKLY BOUNDED PETRI NETS; AWPN '06

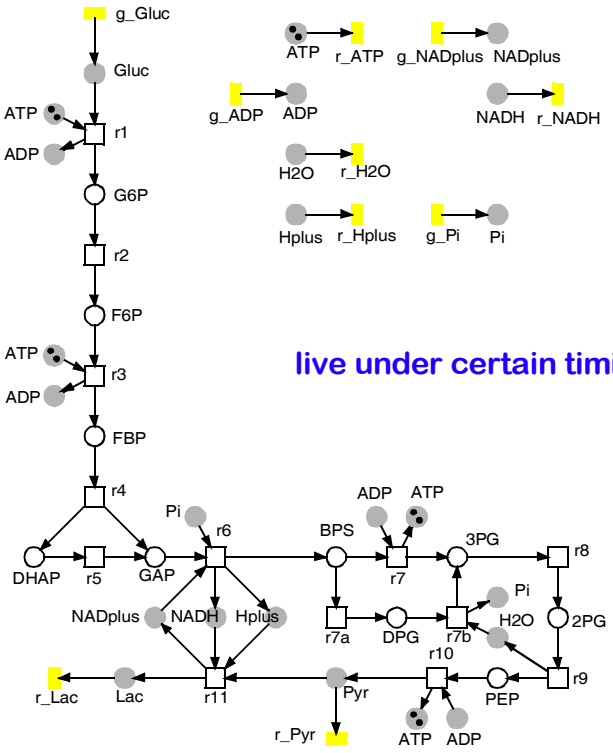
TIME-DEPENDENT BOUNDEDNESS

- given: **time-free Petri net**
  - -> *unbounded*
  - -> *live (supposed to be)*
- wanted: **corresponding time-dependent Petri net**
  - -> *bounded*
  - -> *(still) live*
- **questions**
  - -> *for which structures does it work / does it not work ?*
  - -> *are there sufficient / necessary conditions ?*
  - -> *which time windows make the net bounded ?*
  - -> *which time windows preserve a transition sequence's realizability ?*
  - -> *decidability of these questions ?* *-> credits go to Serge Haddad*
- **consistency criterion for (steady state) bio networks**

PROBLEM 2:

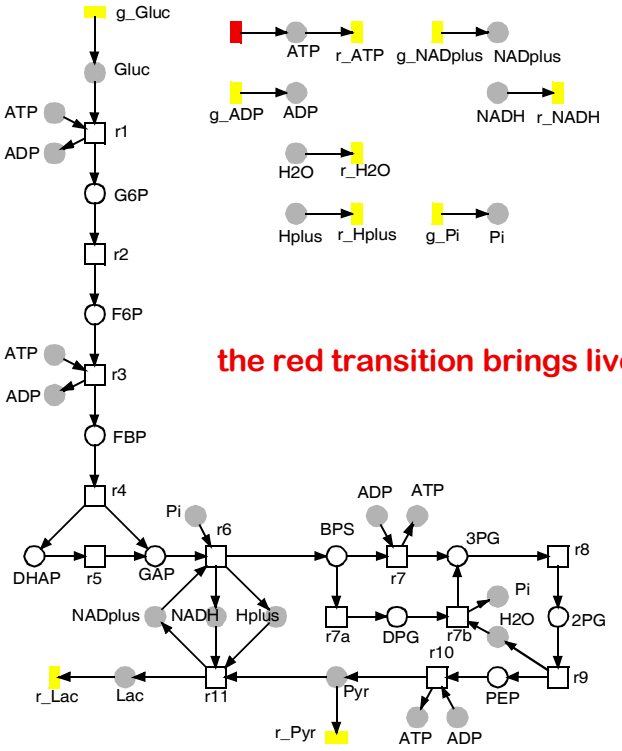
TIME-DEPENDENT LIVENESS

EXAMPLE - GLYCOLYSIS



live under certain timing constraints

EXAMPLE - GLYCOLYSIS



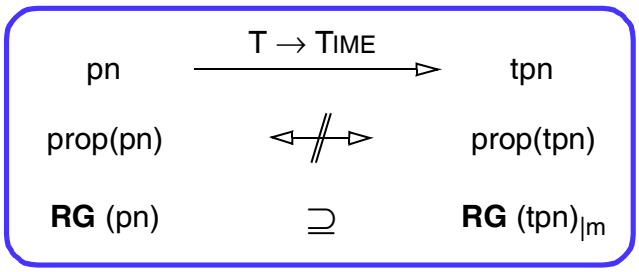
the red transition brings liveness under any timing

SUMMARY, TWO OPEN PROBLEMS

- **problem 1: time-dependent boundedness**
  - -> *given:* *unbounded and live time-free Petri net*
  - -> *question:* *under which conditions are there time restrictions, making this Petri net bounded, while preserving liveness ?*
- **problem 2: time-dependent liveness**
  - -> *given:* *non-live time-free Petri net*
  - -> *question:* *under which conditions are there time restrictions, making this Petri net live ?*

-- especially helpful for analyzing bio Petri nets --

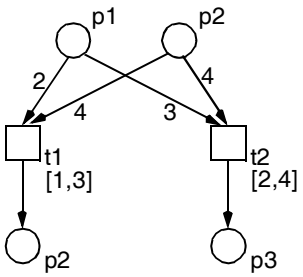
- **time may restrict the behaviour**



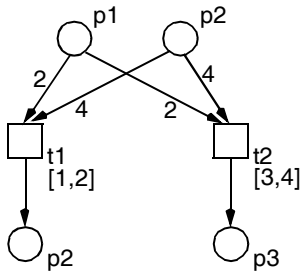
- **time may influence qualitative properties**

TIME-INSENSITIVE PROPERTIES	TIME-SENSITIVE PROPERTIES
BND (pn) -> BND (tpn)	not BND (pn) -> BND (tpn)
not DSt (pn) -> not DSt (tpn)	DSt (pn) -> not DSt (tpn)
DTr (pn) -> DTr (tpn)	not DTr (pn) -> DTr (tpn)
not REV(pn) -> not REV(tpn)	REV(pn) -> not REV(tpn)

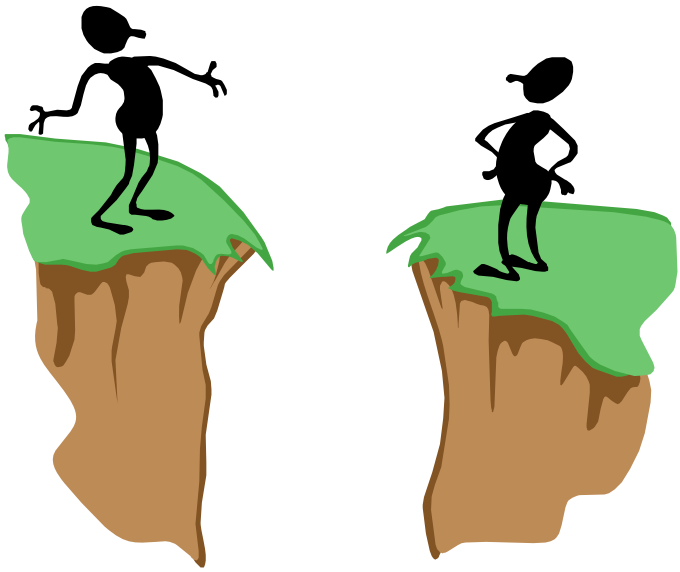
- **net structures, remaining live under any timing**
  - -> *persistent (dynamically conflict free) nets*
- **duration nets**
  - -> *ES*
- **interval nets**
  - -> *earliest firing time of all transitions is zero*
  - -> *latest firing time of all transitions is infinite*
  - -> *well-formed EFC*
  - -> *well-formed behaviourally free choice, i.e., t1 # t2: AG (enabled (t1) ⇔ enabled (t2))*
  - -> *well-formed ES (?!)*
  - -> *well-formed =*
    homogeneous &
    timely homogeneous &
    no purely immediate transitions



not homogeneous



not timely homogeneous



THANKS !

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